Monitoring of antimicrobial resistance – a national example and EURL-AR experience

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Monitoring of antimicrobial resistance – a national example and EURL-AR experience

Susanne Karlsmose, Denmark

Facts about Denmark

Population: ~ 5.5 mill

Area: 43.098 km^2

Denmark is a major livestock producer in Europe

- and the worlds' largest exporter of pork

In 2008,

~ 5.800 pig farms (12.7 million pigs)

~ 5.200 dairy farms (575.000 dairy cows (1.6 million cattle in total))

~ 300 with specialised poultry production (3.5 million hens)

- Highly specialised – only 3% has more than one animal species

(The Ministry of Foreign Affairs in Denmark and Danish Agricultural and Food Council)

Classes of antimicrobials used in agriculture

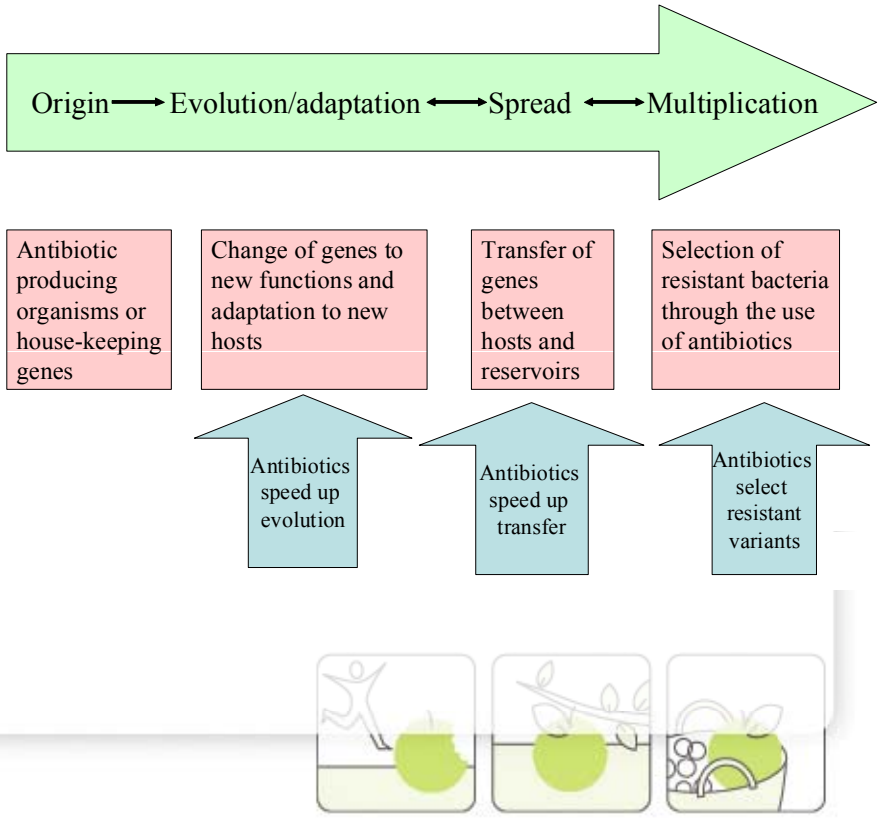
All classes are also used in humans, including substances considered Critically Important Antimicrobials by WHO for human therapy (e.g. fluoroquinolones, 3rd gen. cephalosporins, streptogramins)

- very few exceptions

Emergence of resistance

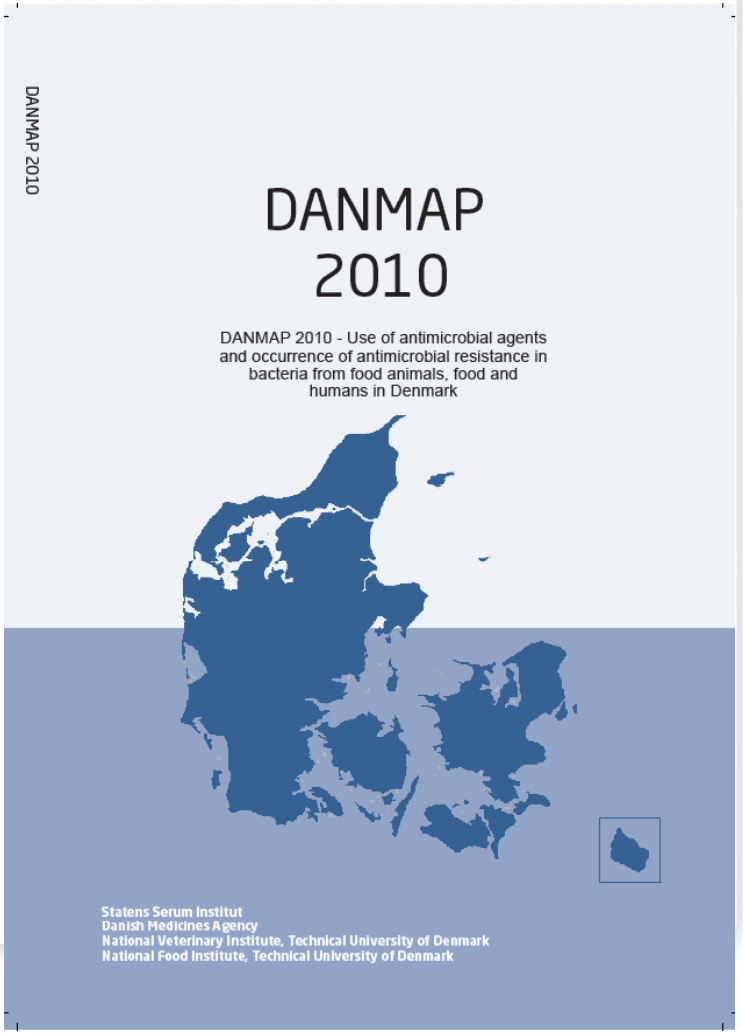
What can we do to control it???

- Monitoring of resistance
- Association between antimicrobial use and resistance
- Spread of resistance from animals to humans
- Global spread of foodborne pathogens
- Basic evolution to understand global epidemiology



DANMAP

Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark



The DANMAP programme

- Initiated in 1995
  (First report in 1997)
- Objectives
  - Monitor consumption of antimicrobials for food animals and humans
  - Monitor the occurrence of antimicrobial resistance among bacteria from food animals, food of animal origin and humans
  - Study associations between antimicrobial consumption and antimicrobial resistance
  - To identify routes of transmission and areas for further research

The DANMAP participants

- Statens Serum Institute
- (The Danish Veterinary and Food Administration)
- The Danish Medicines Agency
- National Food Institute, Technical University of Denmark
- National Veterinary Institute, Technical University of Denmark

The results are published annually

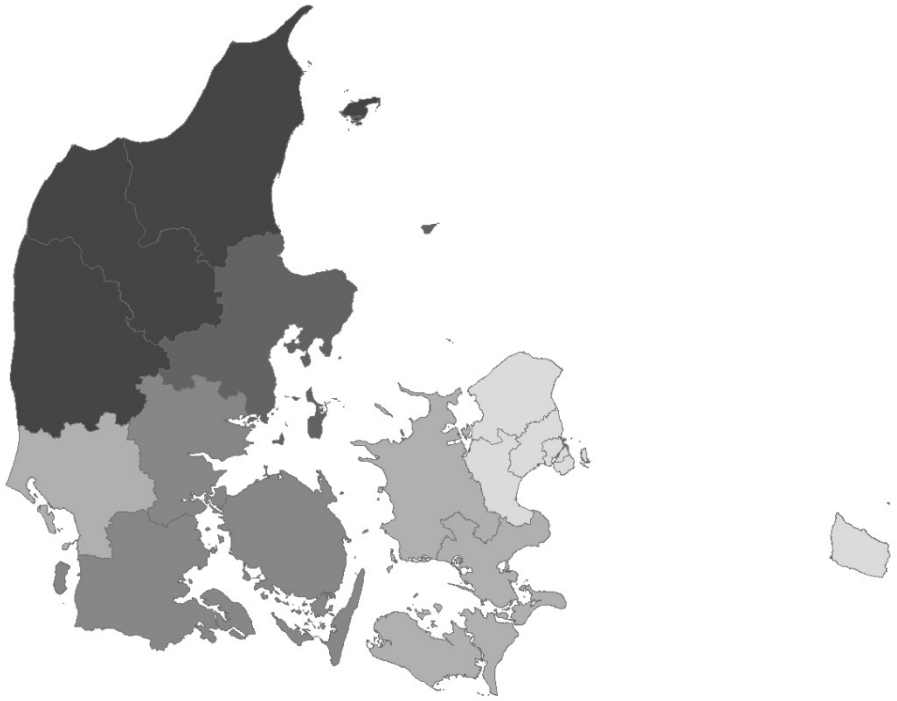
Considerations (1)

- Purpose of the surveillance programme
  - Trend
  - Early warning
  - Estimate associations between consumption and resistance
  - Effect of interventions
  - Guide to antimicrobial use policies
- Methods
  - identical methods
  - MIC-values
- Active / passive surveillance

Considerations (2)

- Sampling scheme
  - The sampling frame should cover all epidemiological unit of the national production
  - A representative sample collected randomly
    - The epidemiological unit for broilers and turkeys is the flock
    - For pigs and cattle the epidemiological unit is the holding
  - Sampling procedure remains constant
- Comparable samples between populations

Herds 2002-2006



DANMAP Herds 2002-2006

Passive surveillance

Diagnostic submissions from veterinarians and human doctors

Isolates from the existing *Salmonella* surveillance programmes

Advantage and disadvantage:

- Low cost, large number of isolates
- Representing worst cases, often not a representative sample

Active surveillance

Extra samples that are collected on our request, we design the sampling strategy

The samples are from healthy animals, humans and from foods (slaughterhouses, retail outlet e.g. supermarkets)

Advantage and disadvantage:

- Knowledge about the level of resistance in the normal population and in food, we have influence on the sampling scheme
- Each sample has a price, often not a large number of isolates

Isolates from food animals

- Random sampling of herds at slaughter
  - Broilers - 95% of population
  - Pigs - 95% of population
  - Cattle - 90% of population
- Diseased population
  - Used to be almost 100% national coverage of poultry, pigs and cattle
  - Decreasing coverage over the past decade

Isolates from food

- Samples are collected from pre-determined categories
- Nationwide collection of samples at wholesale and retail outlets
- Imported foods are sampled for *Salmonella* at point of entry

Isolates from humans

- Results of routine testing of various pathogens in fourteen major hospitals
- Data from testing of *Campylobacter* and *Salmonella* submitted to the central public health laboratory
- Enterococci and *E. coli* isolated from stools from approx. 200 healthy humans
  (random sample 2004-2007; recruits 2008)

Bacteria included in the DANMAP programme

Genus	Indicator	Pathogen	Zoonotic
E. coli	+	+	
Enterococci	+		
Staphylococci		+	
Streptococci		+	
Salmonella			+
Campylobacter			+

EU and Danish government interventions - I

- Since before the 1970s all veterinary medical products have been prescription only
- In 1994 the Central Husbandry Register (National Animal Identification System) was established, with national registration and identification of every herd in Denmark
- In 1994/95 any prophylactic use of antimicrobials was prohibited and the veterinarians' profits from direct sales of medicine were fixated at a very low level with a maximum of 10%
- In 1995 preventive veterinary strategies were implemented with herd health contracts on a voluntary basis and regular monthly visit from the veterinarian, irrespective of the actual herd health situation, in order to promote preventive veterinary strategies, optimizing antimicrobial use
- In 1995 the DANMAP programme was established

EU and Danish government interventions - II

- In 1995, the Danish government banned the non-therapeutic use of avoparcin for growth promotion in Denmark (was extended to all EU countries in 1997)
- In January 1998, the Danish government banned the non-therapeutic use of virginiamycin for growth promotion
- In December 1998 the EU implemented an overall ban of virginiamycin, bacitracin, tylosin and spiramycin for growth promotion
- In 2000, VetStat was established, recording every antibiotic prescribed to production animals
- In 2002 fluoroquinolones were restricted to only be used if a current laboratory test shows that no other antibiotics can be used for that disease in that herd of production animals
- In 2002, EU voted to phase out all non-therapeutic use of antibiotics for growth promotion as of the beginning of 2006

EU and Danish government interventions - III

- Action plan 2005 for reduction and prudent use of antimicrobials in swine, including

  - treatment guidelines for swine veterinary practitioners

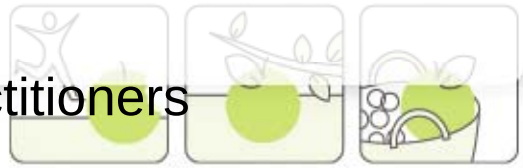
  - direct risk communication with the individual swine veterinary practitioners with a high prescription rate

- Action plan 2007 for reduction and prudent use of antimicrobials in cattle, swine and poultry, including

  - direct risk communication including audit and supervision of prudent use of antimicrobials, every second year, of all veterinarians working with food-producing animals

  - a task force was established in order to secure that there are no economical relationships between veterinary practitioners and the pharmaceutical industry

  - treatment guidelines for cattle veterinary practitioners



EU and Danish government interventions - 2010

- Evidence based – including pharmacokinetics and –dynamics - novel treatment guidelines for swine veterinary practitioners
- A joint Antimicrobial and Resistance action plan between the Ministry of Health and the Ministry of Food, Agriculture and Fisheries
- Establishment of threshold values for acceptable herd levels on mortality, antibiotic usage and certain welfare parameters in swine and cattle and enforced control in herds with levels above the threshold values
- Mandatory action plans for reduction of antibiotic usage in swine herds above the threshold value for antibiotics usage – the so-called 'yellow card' initiative

Guidelines for veterinary practitioners:

Evidence-based prudent use guidelines for antimicrobial treatment of pigs

May be used as a working tool

⇒ To optimize antimicrobial usage

⇒ To look up a specific disease and pathogen in the guidelines

⇒ To find, via drop-down lists, products, dosage and treatment period

⇒ To obtain background information/evidence behind

Guideline available for download at www.dvfa.dk

Voluntary actions taken by the Danish agricultural industry

- The Danish cattle and broiler industries voluntarily stopped the non-therapeutic use of all antibiotics for growth promotion in February 1998
- The Danish swine industry voluntarily stopped all non-therapeutic use of antibiotics in swine above 35 kg by April 1998, and for all age groups by January 2000
- The Danish swine industry enforced a voluntary ban on all usage of the high-risk antibiotics cephalosporins from 1. July 2010 (two-year ban)

Legislation regarding veterinary use of antimicrobial agents since 1993 - I

- Order (DK) 142/1993: Restricted the use of extemporaneously prepared medicines; also called the cascade rule, imposing mandatory first priority to medicinal products approved for the relevant species, subsidiary approved for other species.
- Directive (DK) 60/1995: Limits the veterinarians' profit when distributing medicines to a maximum of 5–10% at sales.
- Order (DK) 303/1995 and 304/1995: Limit the veterinary prescription to a maximum of 5 days of treatment in production animals. Exceptions only granted when a veterinary advisory service contract between the veterinarian and the farmer was signed. In those cases, up to 35 days of treatment is allowed for a diagnosed disease or a disease that was expected in the pigs, calves and poultry, on the basis of the veterinarian's knowledge of the herd (revised by Order (DK) 785/2010). By July 2010, veterinary advisory service contracts became obligatory for all larger pig and cattle herds in DK

Legislation regarding veterinary use of antimicrobial agents since 1993 - II

- Order (DK) 303/1995: Treatment allowed only in diseased animals or animals in a well defined incubation period (metaphylaxis) and prophylactic use became illegal (revised by Order (DK) 910/2006).
- Mandatory registration by the veterinary practitioners of used, delivered and prescribed drugs to farmed animals. The information must be available for inspection by veterinary officials for 3 years). Since 2001, reporting into the VetStat database has been mandatory.
- Order (DK) 285/1996: Pharmacies and the pharmaceutical industry prohibited from offering economic incentives to veterinarians or others for the purpose of increasing product sales.

Legislation regarding veterinary use of antimicrobial agents since 1993 - III

- Order (DK) 119/2002: Fluoroquinolones intended for injection were restricted to use by the veterinary practitioner only.
- Order (DK) 134/2003: Mandatory susceptibility testing in relation to use of fluoroquinolones for production animals, documenting the need. Notification of use of fluoroquinolones to the authorities is mandatory.
- Order (DK) 1319/2010: The "yellow card" control of antimicrobial use in the pig production, imposing preventive measures in the herds with highest consumption per pig. In July 2010, an information letter about the upcoming "yellow card" was sent to the pig farmers, using the 20% highest number of ADD's per pig.

Better Training for **Safer Food**

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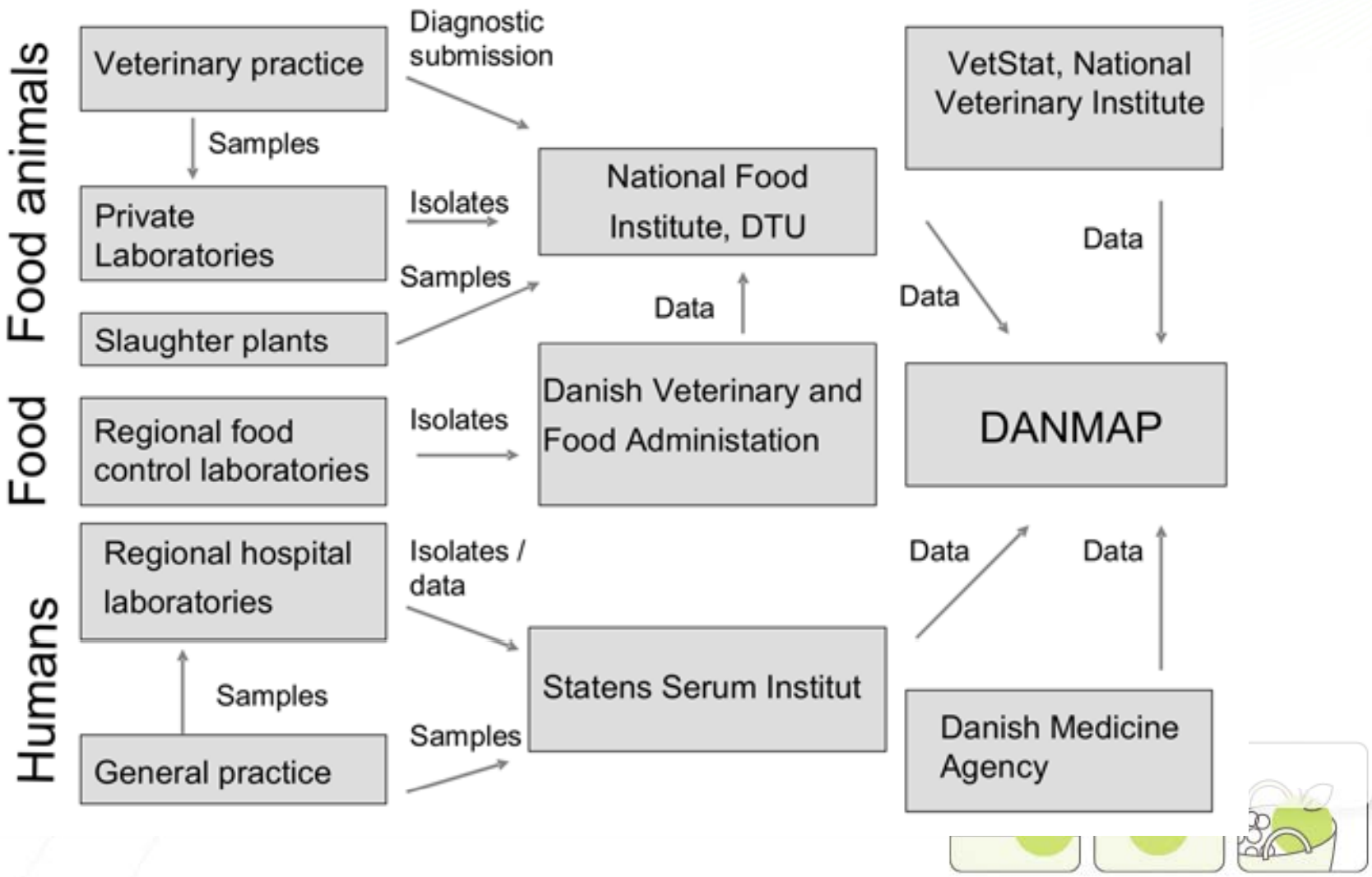

Running costs: < 1 mio. USD/year

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Drug statistics before 2001

- ✓ have enabled us to demonstrate the effect of AGP intervention on antimicrobial resistance
- ✓ have provided information on overall trends in usage
- ❖ have NOT provided information on usage in target animal species
- ❖ detailed modelling of effect of usage on resistance has not been possible

VetStat - National monitoring of veterinary medicine use

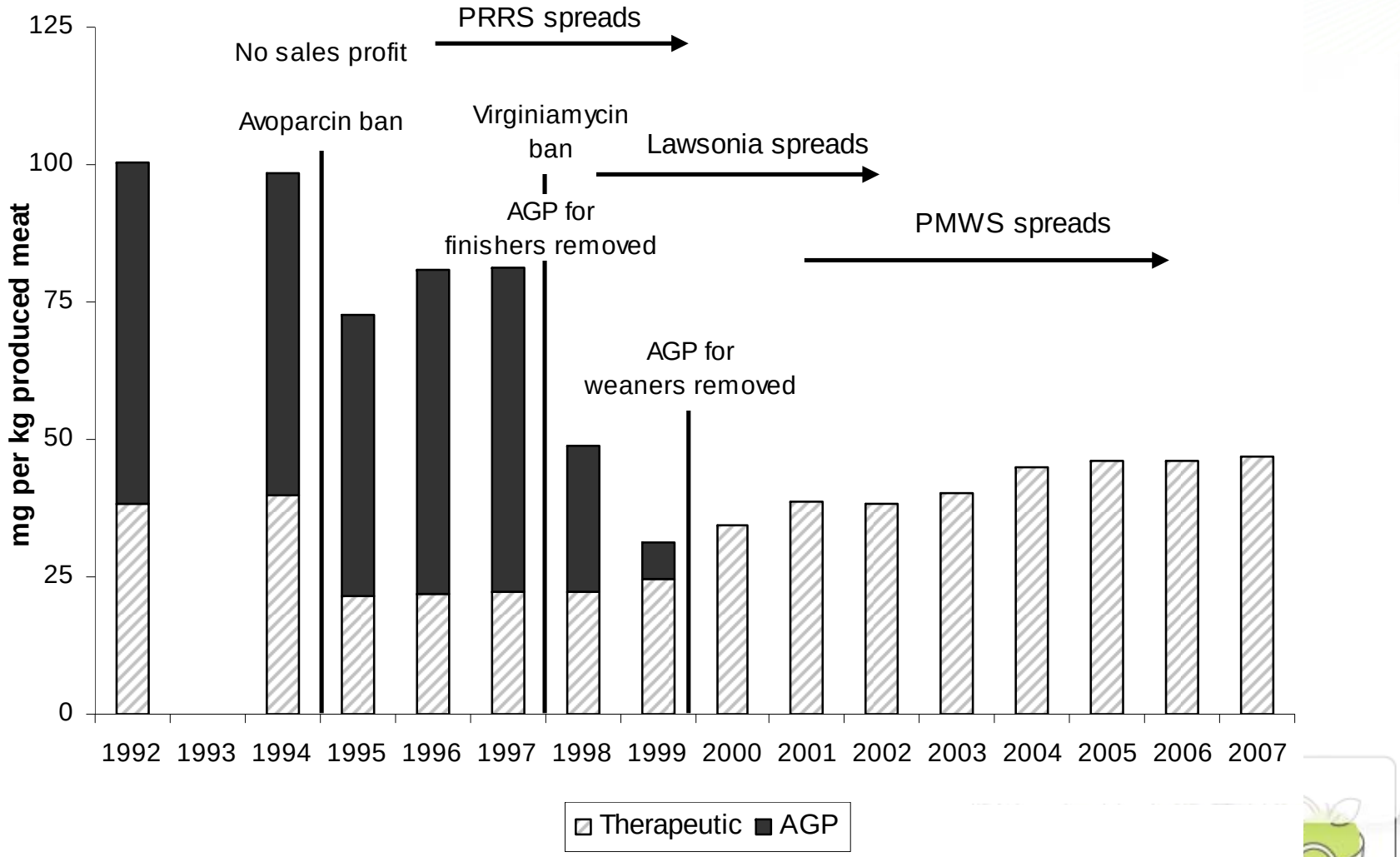
- All therapeutic medicines and medicated feeds (since 2001: coocidiostatics for poultry)
- Valid data from 2001 and forwards
- Information on user level and about prescriber

For each record:

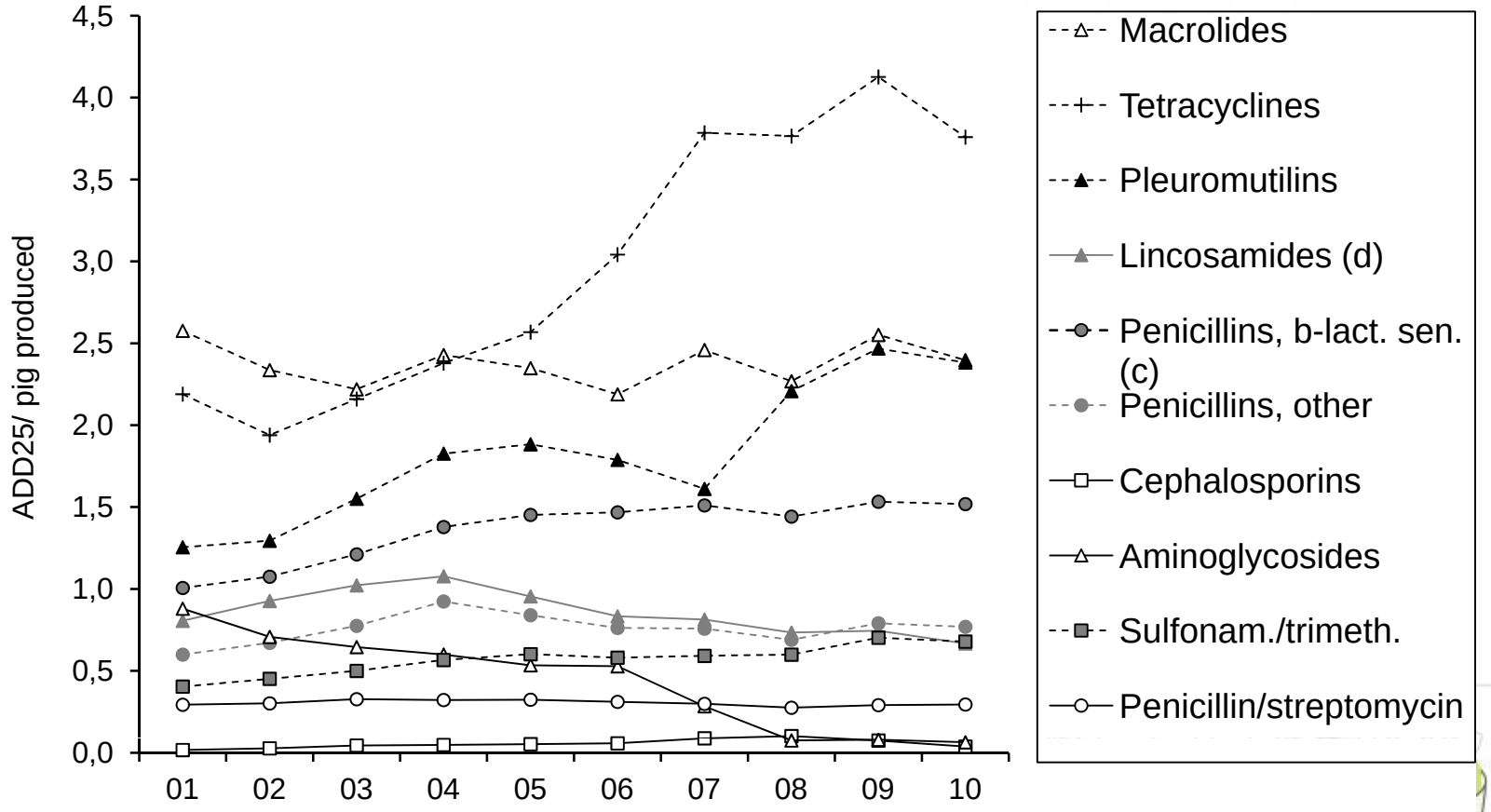
- Farm ID
- Animal species
- Age group
- Disease category
- Date
- Drug ID
- Drug quantity
- Prescriber ID

Running costs: ~0.5 million € per year

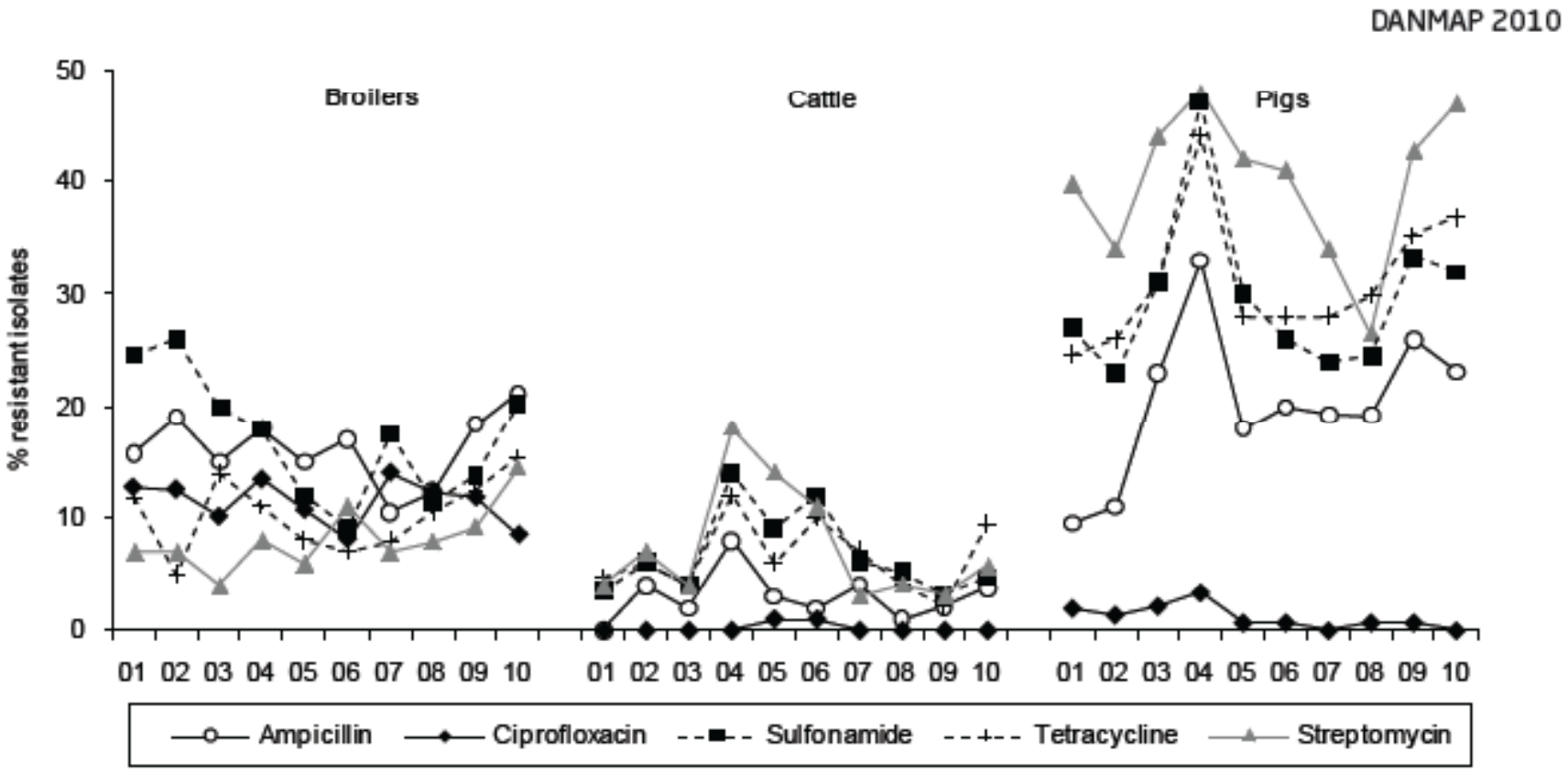
Trends in antimicrobial use in pigs (mg/kg bw)



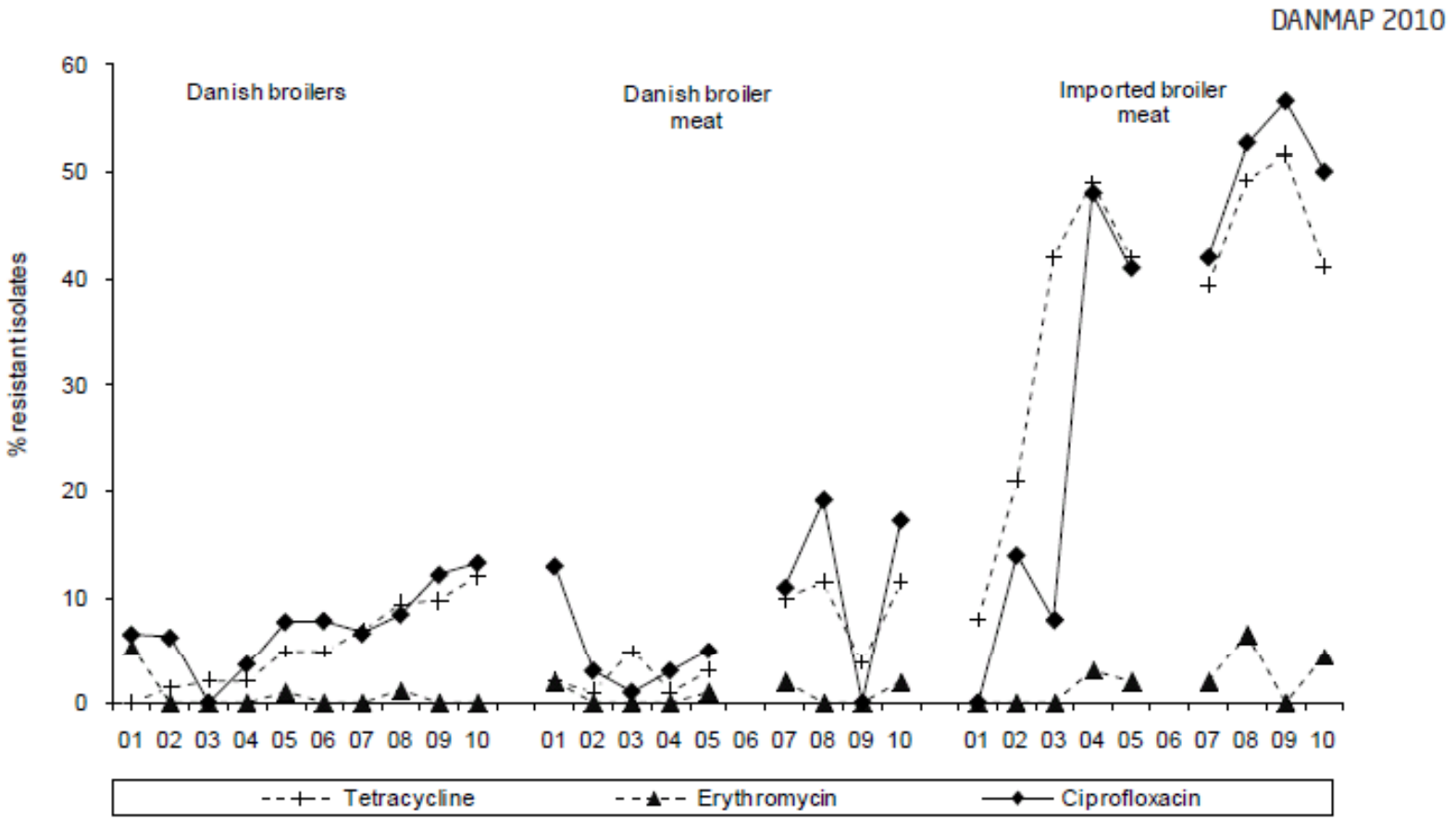
Trends in antimicrobial use for pigs, Denmark



Resistance (%) in indicator *E. coli*

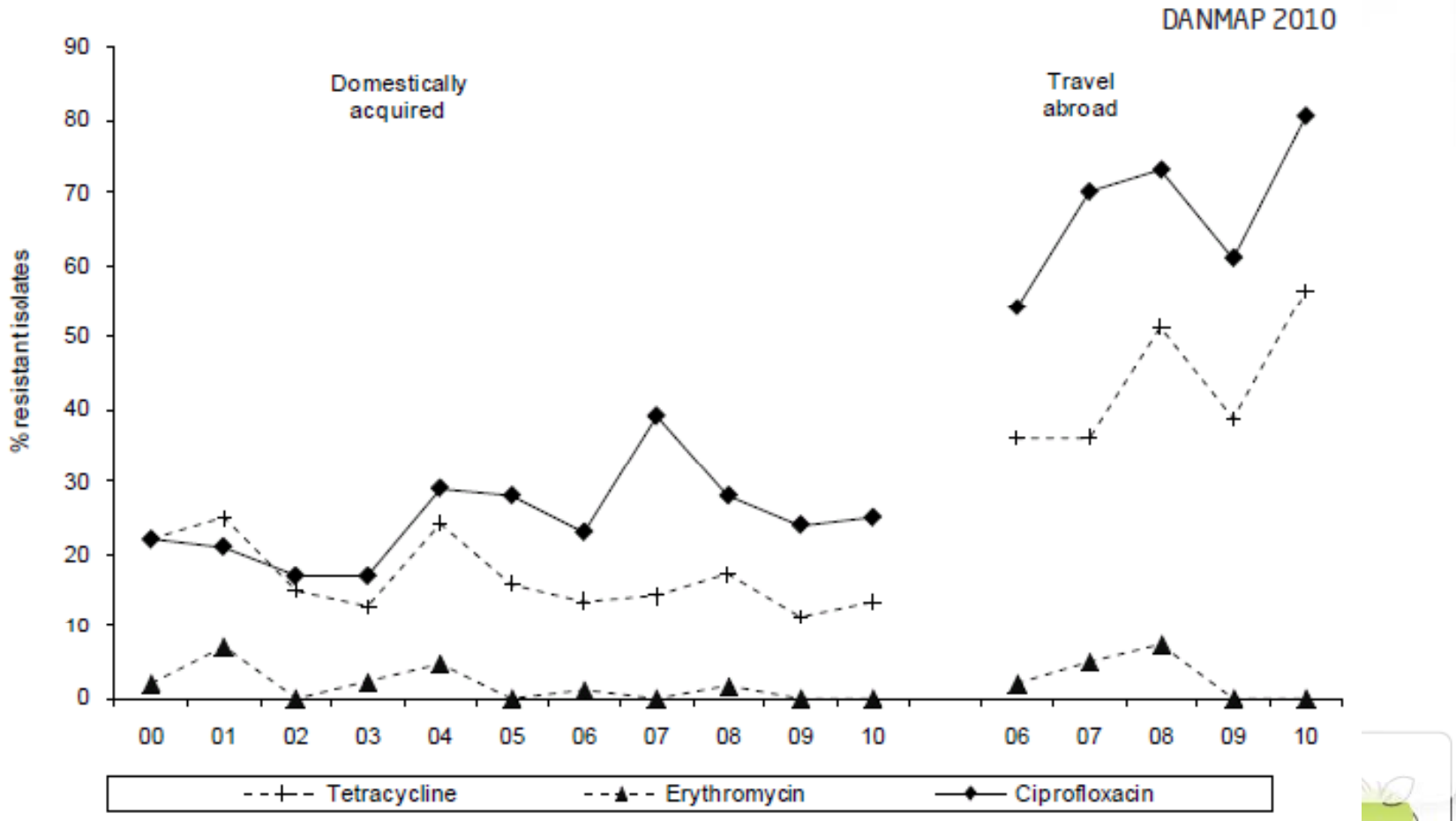


Resistance in *Campylobacter jejuni* - I



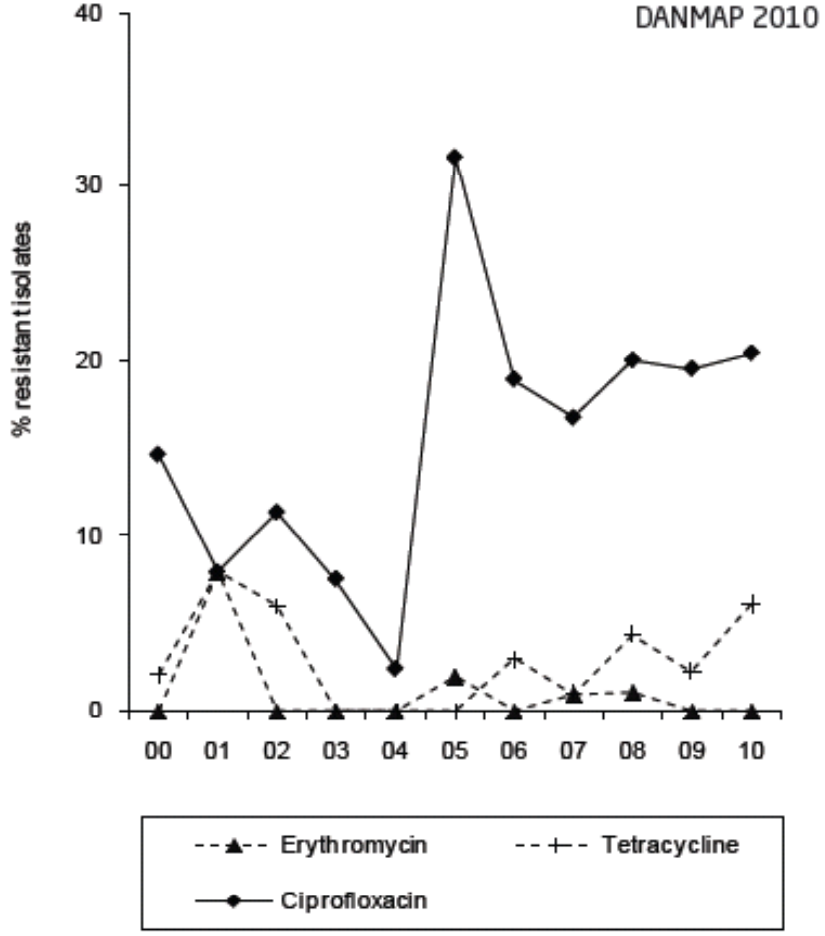
Campylobacter jejuni – II

Resistance (%) in *C. jejuni* from human cases, Denmark



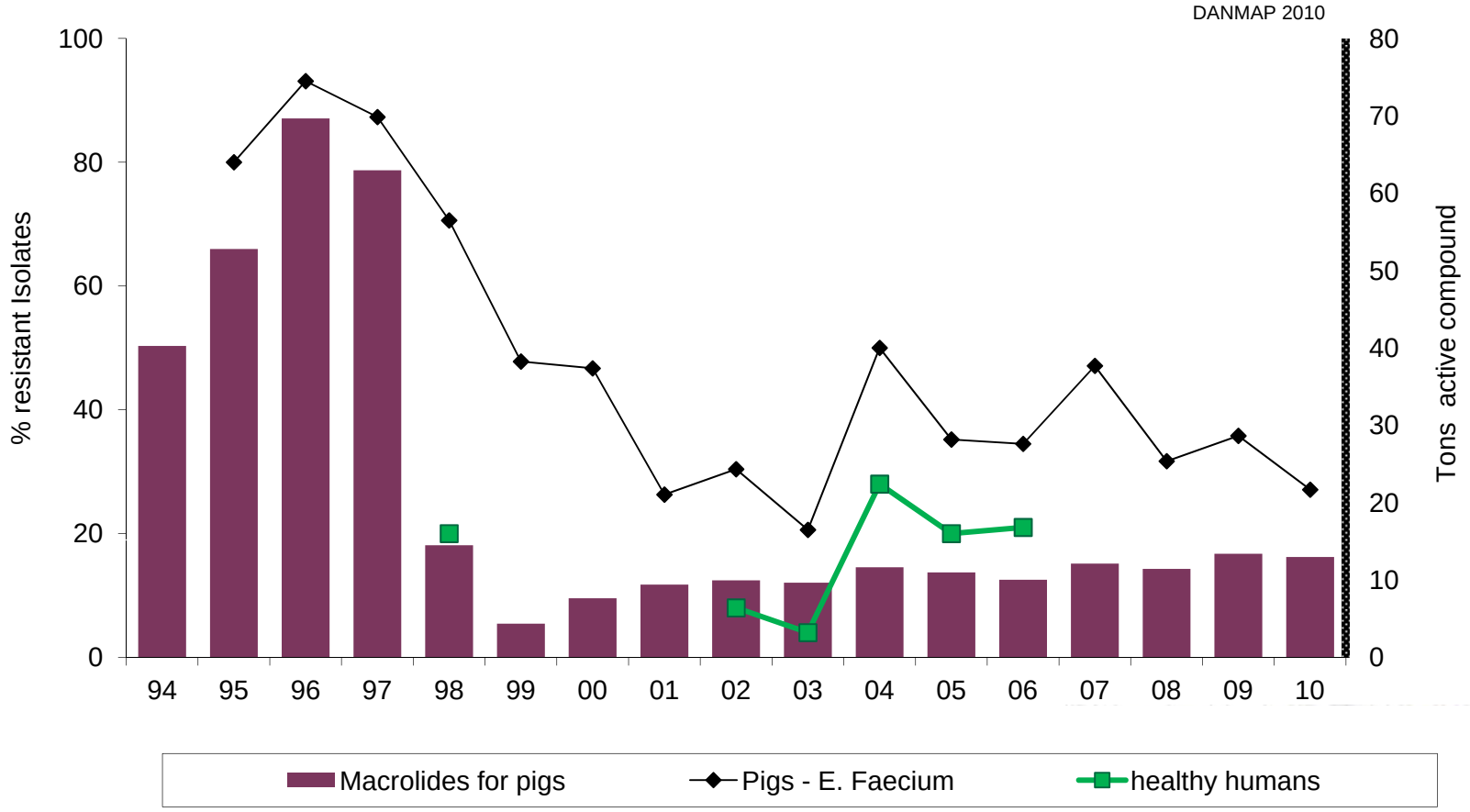
Campylobacter jejuni – III

Resistance (%) in *C. jejuni* from cattle, Denmark



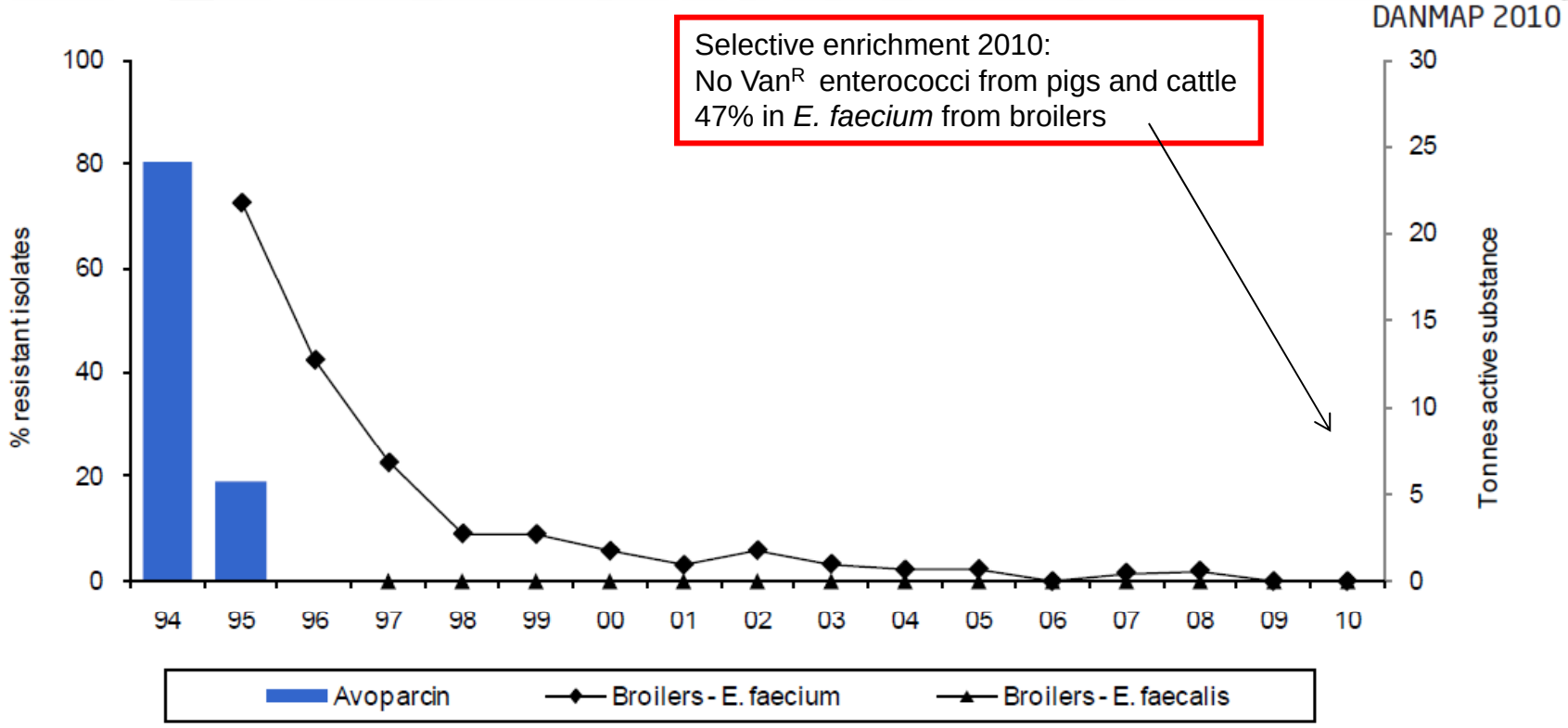
Effect of interventions:

Resistance to erythromycin
among *Enterococcus faecium* from pigs and humans
and the consumption of macrolides in pigs



Effect of interventions:

Resistance to avoparcin and the consumption of avoparcin in broilers



VREF exist even 15 years after the ban!
=> introduction of a drug can lead to resistant bacteria which may increase if the drug is reintroduced

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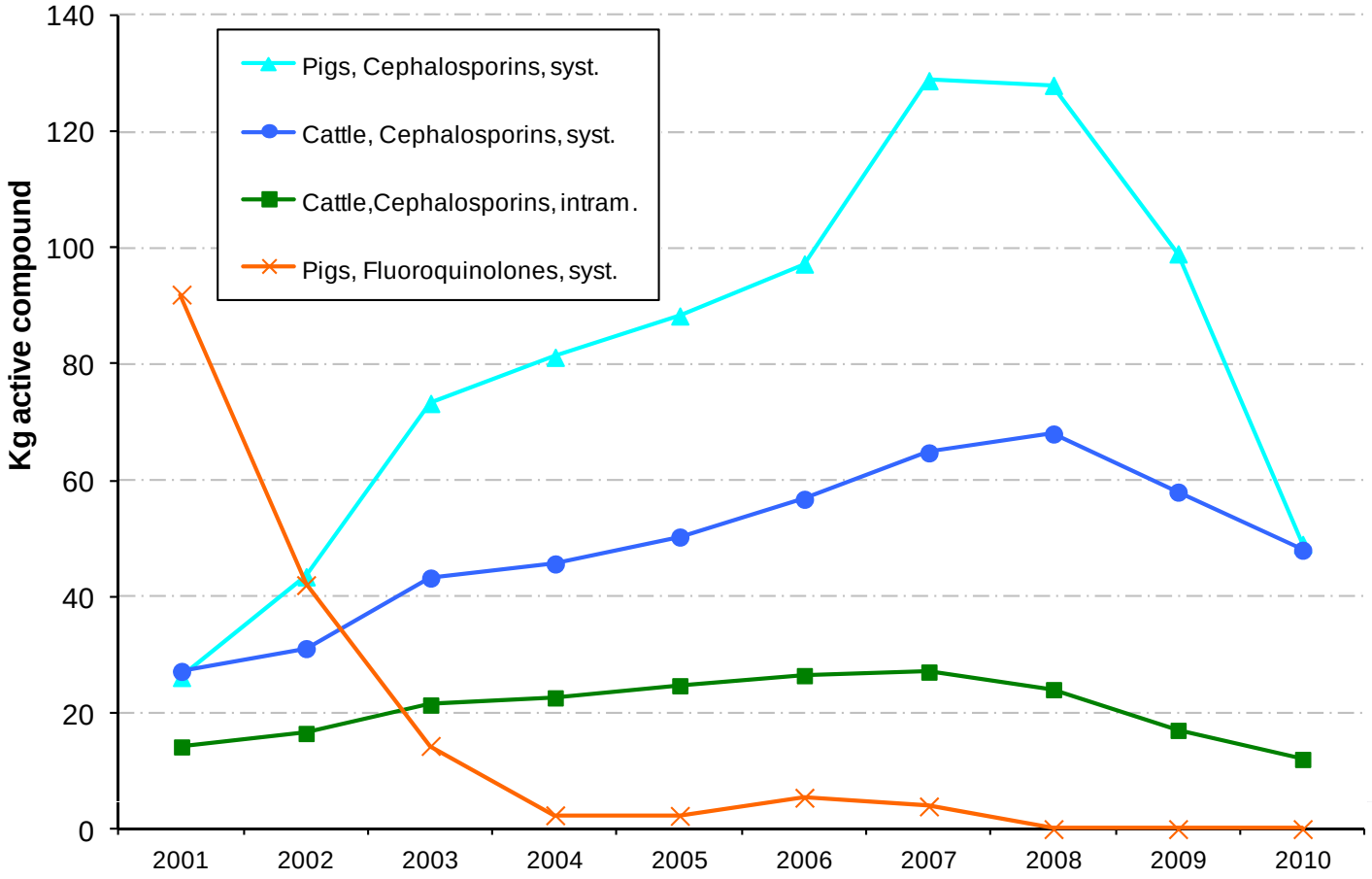
Effect of interventions:

cephalosporines (3. og 4. gen) and fluoroquinolones



Development over the years (1)

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- Still contains:
  - 'basic surveillance', consumption and prevalence of resistance in zoonotic bacteria and indicator bacteria, and pathogens
  - Looks at relations between consumption and resistance
  - Strong integrated aspect in all relevant parts of the report
- Previously:
  - More focus on veterinary pathogens
  - Only phenotypic testing of bacterial isolates

Development over the years (2)

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- Now:
  - More focus on emerging resistance (MRSA and ESBL)
  - Zoonotic importance of other bacteria (*Clostridium difficile*)
  - Zoonotic importance in indicator bacteria (*E. coli* and *enterococcus* spp.)
  - More focus on epidemiology (origin of meat, travel relations, geography)
  - Focus areas and textboxes with supporting information and studies
  - More typing and genotypic testing

Why the changes?

- Change in diagnostic testing from public to private laboratories
- Change in other programmes that affect the passive sampling
- New resistance problems
- More trade and travel activity
- Better tools and genetic methods

Spread of ESBL worldwide – more focus

- Extended spectrum beta lactamase (ESBL)-producing bacteria are one of the fastest emerging resistance problems worldwide
- Use of 3rd and 4th generation cephalosporins may select for ESBL

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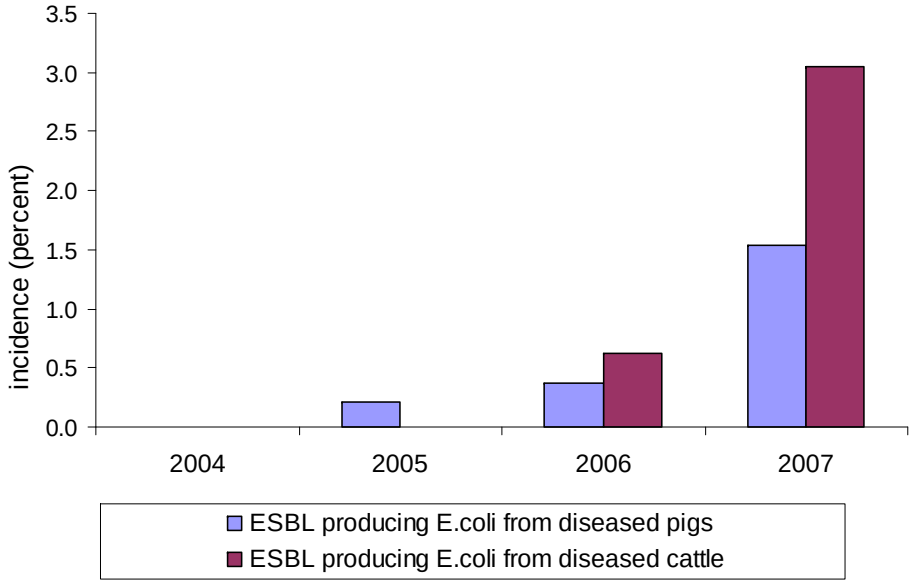
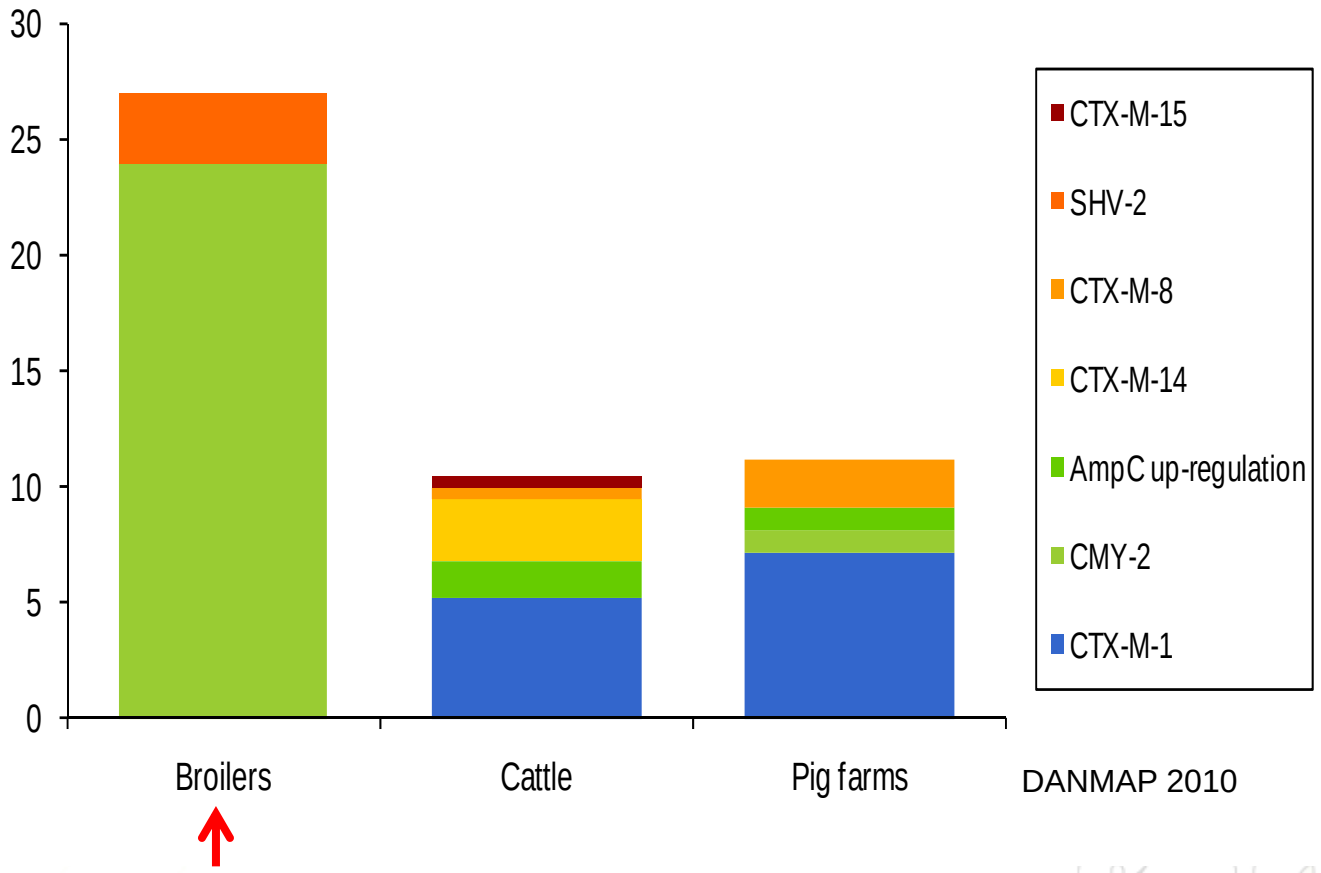
ESBL-producing bacteria from animals

- Until August 2003 ESBL-producing *E. coli* and *Salmonella* from animals and food was not detected in Denmark
- The first cases of ESBL-producing bacteria was found in imported food and animals
- In 2005, the first ESBL-producing *E. coli* was detected in Danish animals
- In 2006, ESBL-producing *E. coli* was detected in 7 cases and in 2007 it was 23 cases



ESBL *E. coli* in broilers, cattle and pig farms, 2010



Cephalosporins have not been used for broilers in DK for at least 10 years

Results: Prevalence (%) of ESBL in raw meat 2009 and 2010 – selective enrichment

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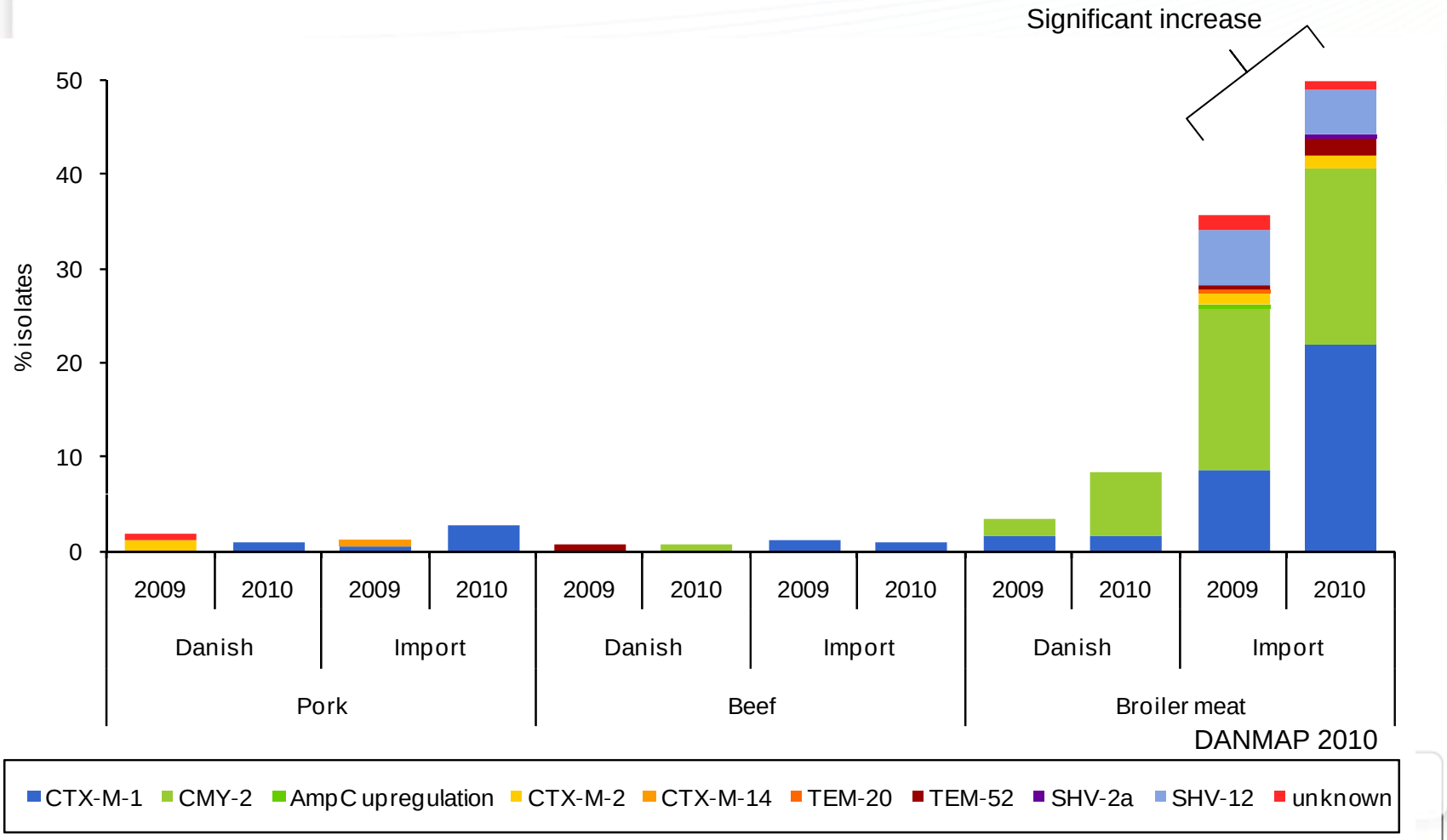

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Summary (ESBL)

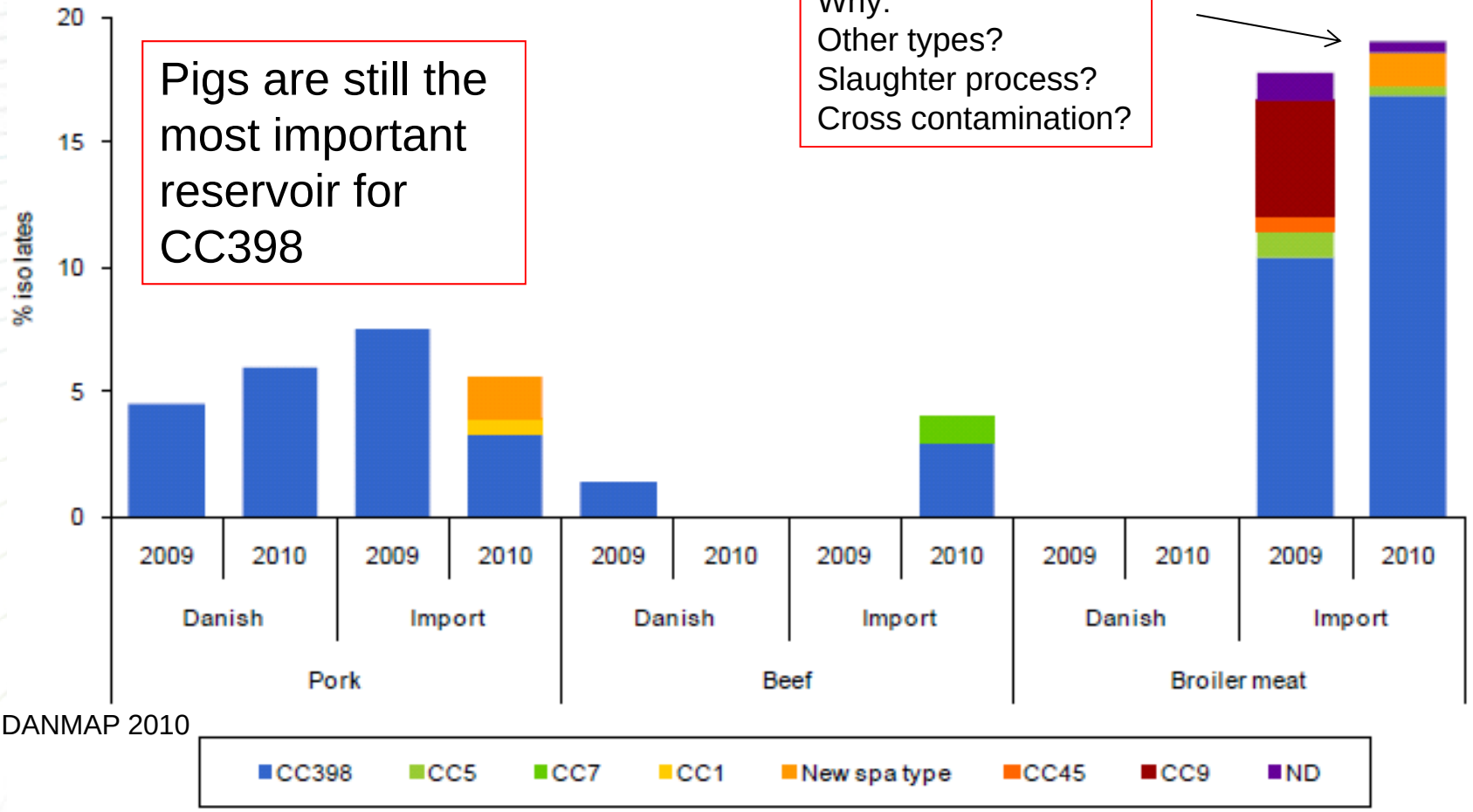
- The use of more sensitive method (selective enrichment with ceftriaxone) revealed ESBL-producing *E. coli* , which were not found by standard monitoring
- The most important meat source seemed to be imported poultry meat. In addition, a high occurrence was found in Danish broilers at slaughter and cephalosporins have not been used for at least 10 years
- As certain genotypes were dominant in *E. coli* from certain sources the genotype may be valuable for source attribution
- Some of the genotypes found among isolates from meat/animals are also found among *E. coli* causing infections in humans

MRSA in production animals and meat

- Pigs at slaughter in 2009 13% MRSA, 95% with CC398
- Pigs stables in 2010 16% MRSA, no in broilers or cattle at slaughter

Pigs are still the most important reservoir for CC398

Why:
Other types?
Slaughter process?
Cross contamination?



DANMAP 2010

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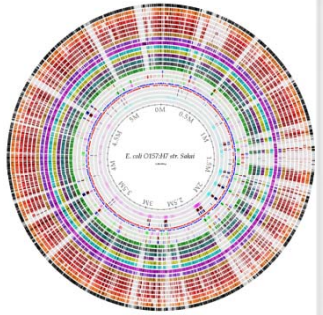
In the future

DANMAP will develop towards use of more genetics methods

– E.g. based on total sequencing



At DTU, we have are currently running a 36 mill DKK project to develop the bioinformatics tool in a project called **Center for Global Epidemiology** (CGE).

- The zoonotic aspect will be broader/different (*E. coli*, enterococci, *S. aureus* (MRSA CC398), *C. difficile*)
- More details about epidemiology and virulence
- Better addressing of co-selection

Meanwhile:

- Avoid use of critically important drugs as much as possible
- Keep the total consumption as low as possible

Summary, DANMAP

- DANMAP provides a baseline for antimicrobial resistance
- DANMAP records trends in antimicrobial resistance
- Overall, levels of antimicrobial resistance reflect consumption of antimicrobials
- With VetStat the possibility to demonstrate association between the use of antimicrobial agents and resistance is improved
- A tool to follow national interventions

The EURL-AR

Research group for antimicrobial resistance and molecular epidemiology

- 2 Professors
- 12 Scientists
- 8 PhD-students
- 10 Technicians

1/3 Advisory tasks + Teaching
2/3 Research

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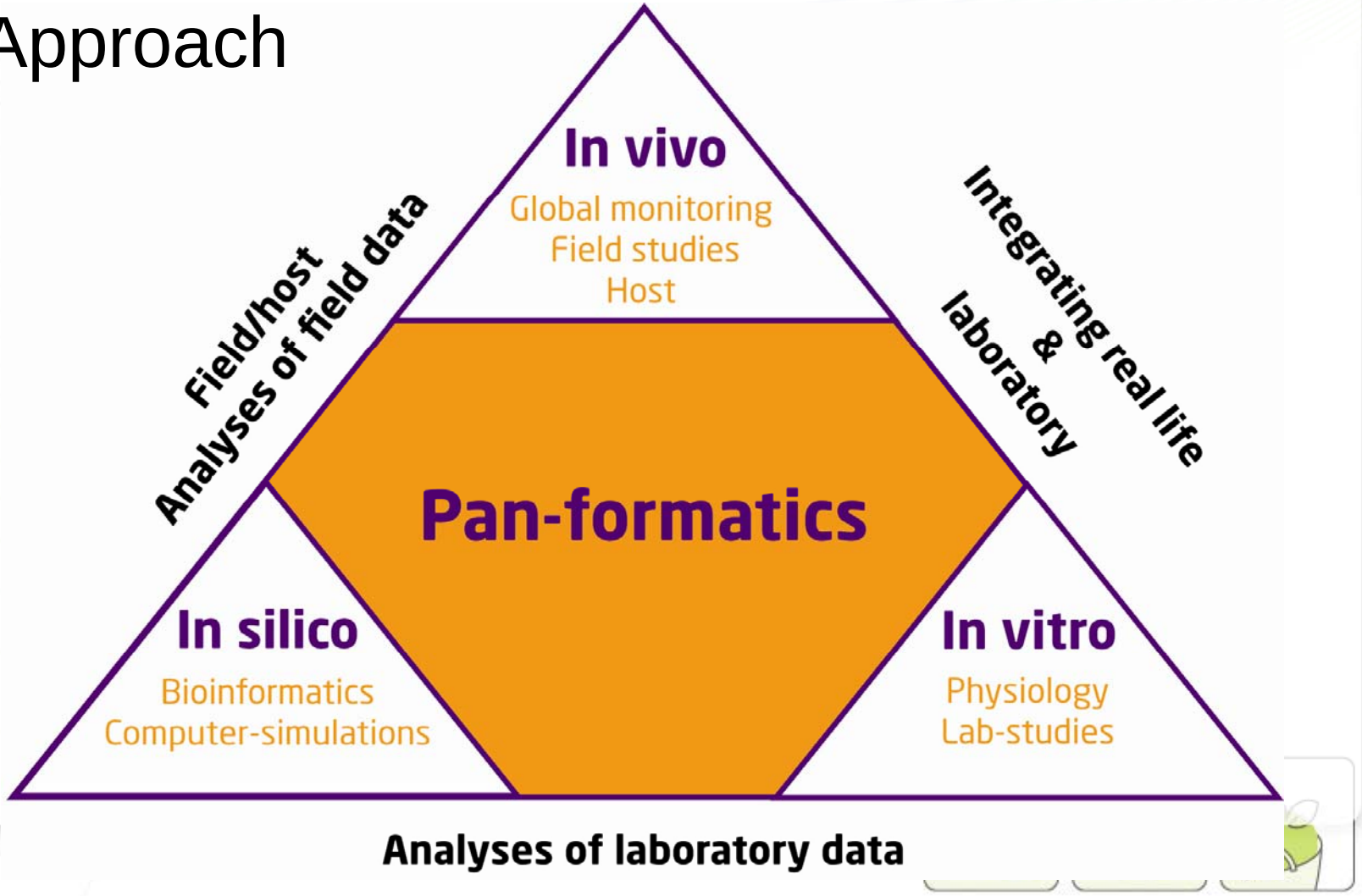
Approach



Why an EURL-AR?

- The main purpose
  - to ensure the quality of antimicrobial susceptibility testing in the Member States
  - to harmonise the procedures and methodologies used

- Activities aim at implementing, from an analytical point of view, the provisions of monitoring of antimicrobial resistance set down in Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents

Tasks of the EURL-AR

- Scientific advice and support to the EU Commission
- Co-ordination of National Reference Laboratories and provision of technical support
  - Contact to the network of NRL's
  - Annual workshops, training courses, site visits
  - Dissemination of knowledge and information (www.eurl-ar.eu)
  - Collection of information on activities at the NRL's
- Proficiency tests and quality assurance
- Confirmatory testing
- Evaluation and development of analytic methods

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WHO Global Foodborne Infections Network

→ Steering Committee

CDC Centers for Disease Control and Prevention

World Health Organization

DTU Food National Food Institute

ecdc European Centre for Disease Prevention and Control

National Institute of Public Health

ozfoodnet

international network Institut Pasteur

Public Health Agency of Canada / Agence de la santé publique du Canada

PulseNet International — The International Molecular Subtyping Network for Foodborne Disease Surveillance

University of Utrecht

FDA

Who is GFN?

→ Members

By October 2011: 1722 members from 184 countries

Some of the newest members are from:

- American Samoa
- Burkina Faso
- Comoros
- Cook Islands
- Eritrea
- Iraq
- Lesotho
- Marshall Islands
- Northern Mariana Islands
- Qatar
- Samoa
- Solomon Islands
- Swaziland
- Tajikistan
- Tonga
- Turks and Caicos Islands

Vision and mission

The GFN vision:

A world where all countries prevent foodborne and other enteric infections

…and mission:

To enable countries to detect, control, and prevent foodborne and other enteric infections by:

- *Building capacity for integrated surveillance*
- *Fostering collaboration among human health, veterinary, food and other relevant sectors*

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GFN main activities

- (Inter)national Training Activities
- External Quality Assurance System (EQAS)

External Quality Assurance System (EQAS)

Objectives

- To have laboratories evaluate their performance of serotyping and antimicrobial susceptibility testing (AST)
- To improve quality of surveillance data
- To assess the quality of *Salmonella* serotyping and AST in laboratories worldwide
- To evaluate the effect of the training courses
- To identify barriers for serotyping and AST

Country Databank

Annual national and institutional data is collected:

- Number of *Salmonella* isolates identified/serotyped
- Top 15 *Salmonella* serotypes
- Sources of *Salmonella* isolates

Status, November 2011:

> 1.6 million human isolates

> 450 000 non-human isolates

New user interface under development:

- Include other relevant pathogens
- Include antimicrobial susceptibility patterns
- Include explanatory factors (consumption data, trade, animal production, meteorological data)

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GFN on the web: www.who.int/gfn

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Thanks for your attention!